~~Draft June 24, 2003~~

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

October 21, 2003

OFFICE OF
THE ADMINISTRATOR
EPA SCIENCE ADVISORY BOARD

Note to the Reader:

The attached draft report of the Health Effects Subcommittee (HES) of the Advisory Council on Clean Air Compliance Analysis (COUNCIL) is still undergoing discussion and review. Once discussed by the HES and the COUNCIL at public sessions, and after approval by the COUNCIL, it will be transmitted to the EPA Administrator and become available to the interested public as a final report.

This draft has been released for general information to members of the interested public and to EPA staff. The reader should remember that this is an unapproved working draft and that the document should not be used to represent official EPA or Council views or advice. Draft documents at this stage of the process often undergo significant revisions before the final version is approved and published.

The SAB Staff Office is not soliciting comments on the advice contained herein. However, as a courtesy to the EPA Program Office that is the subject of the review, we have asked the Program Office to respond to the issues listed below. Consistent with SAB policy on this matter, the Council is not obligated to address any responses it receives.

1. Has the Subcommittee adequately responded to the questions posed in the Charge?
2. Are any statements or responses made in the draft unclear?
3. Are there any technical errors?

For further information or to respond to the questions above, please contact:

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Advisory on Plans for Health Effects Analysis Presented in the May 12, 2003 Analytical Plan for EPA's Second Prospective Analysis – Benefits and Costs of the Clean Air Act, 1990-2020: An Advisory by the Advisory Council for Clean Air Compliance Analysis

Insert Date

EPA-SAB-COUNCIL-ADV-03-00x

Ms. Marianne Lamont Horinko
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Advisory on Plans for Health Effects Analysis in the Analytical Plan for EPA's Second Prospective Analysis – Benefits and Costs of the Clean Air Act, 1990-2020:;: An Advisory by the Advisory Council for Clean Air Compliance Analysis

Dear Ms. Horinko:

The Advisory Council on Clean Air Compliance Analysis met on (insert date) to discuss this Advisory provided by its Health Effects Subcommittee on the Agency's plans for health effects analyses in the upcoming Second Prospective Analysis of the costs and benefits of the Clean Air Act. The Health Effects Subcommittee (HES) met in a public session, August 27-29, 2003 to consider in detail charge questions from the Agency related to a wide range of health effects to be addressed in the Second Prospective Analysis.

The Council and the HES are guided in this Advisory by the Agency's charge from Congress in Section 812 of the Clean Air Act Amendments of 1990 that the mandated analyses be "comprehensive" and "that the Administrator shall consider all of the economic, public health, and environmental benefits of efforts to comply. In any case where numerical values are assigned to such benefits, a default assumption of zero value shall not be assigned to such benefits unless supported by specific data."

The Council and the HES provide this advice to assist the Agency in fully characterizing the science related to health effects related to the Clean Air Act. We point out that now, as in the past, major categories of effects will be left unquantified~~have been omitted~~, such as cardiovascular morbidity from long-term exposure, ecological effects and most air toxics health effects, because of the limitations of existing scientific methods and data. The HES appreciates the efforts made by EPA's Project Team to expand benefit categories to be captured in the Second Prospective Analysis in their exhaustive review of a wealth of new scientific literature and their efforts to capture the uncertainties associated with that new literature.

The HES and the Council generally support EPA's Analytical Plan with ~~a few~~two exceptions: (1) the Agency's apparent *apriori* commitment for preferring expert elicitation to other methods for assessing long-term health effects of particulate ~~matter~~ matter; and (2) the omission of infant mortality effects and asthma exacerbation from the base case planned for the study. In regard to expert elicitation, the Council and the HES support investigating this approach in principle as a means to improve the uncertainty analysis. The Council and the HES, however, do not agree that elicitation is necessarily the default approach to be used. There is a need to assess the applicability of this method once the results of the Agency's planned pilot study are evaluated

In regard to the base case for the study, we strongly advise that ~~it~~ the Agency should continue to use prospective cohort studies as the basis for analysis of ~~cohort~~ mortality. We propose the Second Prospective Analysis present the base case with associated uncertainties (preferably confidence intervals of 90% and 10%), plus a set of sensitivity analysis, rather than the base case and a single "alternative analysis." The Council and the HES advise that a single "alternative analysis" to the base case does not represent the comprehensive scientific analysis of health benefits that the Clean Air Act requires. Instead, we advise that the Agency should aim for quantitative estimates that are fair and balanced, with acknowledgement of benefits that can not be adequately quantified at this time. We also support EPA's plans for meta-analysis for ozone mortality and the Agency's plans to consider adding it to base analysis, subsequent to review of the results of those analyses.

We appreciate the opportunity to review the Analytical Plan and to provide you with advice on the analysis of health effects. The HES would be pleased to expand on any of the findings described in this report and we look forward to your response

.

Sincerely,

Bart Ostro, Chair Health Effects Subcommittee	Dr. Trudy Ann Cameron, Chair Advisory Council on Clean Air Compliance Analysis

NOTICE

This report has been written as part of the activities of the EPA Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency. This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names of commercial products constitute a recommendation for use.

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1. EXECUTIVE SUMMARY

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2. INTRODUCTION

2.1. Background on this Advisory

The purpose of this Advisory is to provide commentary and guidance on EPA plans for developing the health effects analysis emissions inventories described in the July 8, 2003 review document, *Benefits and Costs of the Clean Air Act 1990-2020: Revised Analytical Plan for EPA's Second Prospective Analysis* (Analytical Plan).

The Health Effects Subcommittee (HES) of the Advisory Council on Clean Air Compliance Analysis (Council) held a public meeting on August 27-29, 2003 to receive briefings and discuss the charge questions provided by the Agency related to health effects analysis for the Analytical Plan. In addition to the Chair of the HES, who represents the HES on the Council, one additional member of the Council, Ms. Lauraine Chestnut, participated in this meeting. Four other members of the Council's Special Council Panel for the Review of the Third 812 Analysis,[1] who were added to the Council especially to address issues associated with analysis of uncertainty and statistical and subjective probability, joined the meeting either in person, ~~or~~ by teleconference or by providing written comments for consideration during the Subcommittee meeting. In their discussions, members focused on issues related to the Agency's plan to develop health effects estimates.~~emissions inventories~~. The charge questions are discussed in Section 2.2. and listed in Appendix A. The Council held a public meeting on ~~September 23-25, 2003~~(insert date when discussions will happen) to discuss and formalize the advice to the EPA Administrator on this topic.

In its review of the analytical plan, the Council and AQMS are guided by the Council mandate, as identified in the Clean Air Act (CAA) Amendments of 1990,[2]

a) Are the input data used for each component of the analysis sufficiently valid and reliable for the intended analytical purpose?

b) Are the models, and the methodologies they employ, used for each component of the analysis sufficiently valid and reliable for the intended analytical purpose?

c) If the answer to either of the two questions above is negative, what specific alternative assumptions, data or methodologies does the Council recommend the Agency consider using for the second prospective analysis?

[1] Dr. Dr. John Evans, Senior Lecturer on Environmental Science, Harvard University; Dr. Dale Hattis, Research Professor, Center for Technology, Environment, and Development, George Perkins Marsh Institute, Clark University; Dr. D. Warner North, President, North Works Inc; Dr. Thomas S. Wallsten, Professor, Department of Psychology , University of Maryland;

[2] Specifically, subsection (g) of CAA 312 (as amended by Section 812 of the amendments) states: "*(g) The Council shall -- (1) review the data to be used for any analysis required under this section and make recommendations to the Administrator on the use of such data, (2) review the methodology used to analyze such data and make recommendations to the Administrator on the use of such methodology; and (3) prior to issuance of a report required under subsection (d) or (e), review the findings of such report, and make recommendations to the Administrator concerning the validity and utility of such findings.*"

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2.2. Charge Questions Related to Health Effects

Among the thirty-seven charge questions provided to the Council, fourteen charge questions related to health effects, uncertainty analysis of health effects, plans related to data quality and intermediate data products, results aggregation and reporting, uncertainty, stratospheric ozone analysis, and an air toxics case study. These Charge Questions are excerpted from the list of charge questions provided by the Agency on July 8, 2003 and listed in Appendix A to this Report. The charge questions listed there and addressed in this report by the HES retain the numbering scheme provided by the Agency in July. .

3. RESPONSES TO CHARGE QUESTIONS

Agency Charge Question 11. Plans for estimating, evaluating, and reporting changes in health effect outcomes between scenarios

Charge Question 11. Does the Council support the plans described in chapter 6 for estimating, evaluating, and reporting changes in health effect outcomes between scenarios? If there are particular elements of these plans which the Council does not support, are there alternative data or methods the Council recommends?

HES Response: The HES provides here comments not specifically addressed in other formal charge questions posed by the Agency.

a. Ozone effects and issue of covariation with Particulate Matter (PM): The underlying consideration here is whether ozone effects can be added to those based on C-R functions for PM without double counting. In the case of short-term exposure endpoints, the risks of doing so to any substantial extent are small because PM and ozone concentrations tend to be the least correlated of the criteria pollutants. For some endpoints it will be possible to estimate RRs from two-pollutant (ozone and PM) models, where the estimate for each is adjusted for the other. This is one technique, with some remaining possibility for misattribution, to minimize the possibility of double counting. However, since the co-variation of PM and ozone is often low, this is not a requirement. Several studies now suggest that daily exposure to ozone is associated with both daily mortality and morbidity, such as hospital admissions. Some of these findings have been demonstrated in season-specific analysis (Samet et al., 2000) which could then be used in the Section 812 analysis. The HES urges caution, however, in basing estimates on C-R functions derived solely from studies conducted in the northeastern U.S. and southeastern Canada, where ozone and sulfates tend to be highly correlated. To the extent that pollution-specific evidence is drawn from data where the correlations between the pollutants are low, HES suggests that ozone-specific estimates be included in the aggregate estimates.

In the case of long-term exposures and mortality, EPA has correctly decided to not attribute any mortality effects to long-term exposure to ozone given the lack of any supportive of an effect from the original study of the ACS cohort. In addition, the ACS ollow-up study (Pope et al., 2002) found no association between mortality and long-term average ambient ozone concentration.

b. Source-Specific Concentration-Response (C-R) Functions. Regarding the term C-R functions, the Subcommittee notes that Chapter 6 (e.g. pages 6-1 and 6-2) uses the term C-R functions interchangeably for: 1) the concentration-response function epidemiologic studies use to publish to quantify the association and 2) the "impact function" or "attributable case function," which is the function that uses not only the epidemiology-based C-R function but also the

pollution level, the population size, and the baseline frequency of the outcome as input. The Subcommittee advises ***not*** to use one term for both as this creates confusion in discussions of various aspects, including uncertainties (e.g. 'impact function' faces more uncertainties than the C-R function).

There are only a few source-specific C-R functions currently available for species of PM and they are not proposed for use in the Section 812 Analysis. For example, Laden et al. (200x), using source apportionment in the Boston area concluded that traffic-related pollutants and coal combustion-related particles were significantly related to short-term mortality, while soil-derived particles were not, with traffic-related particles having the largest effect. Hoek et al. (2000x) concluded that annual mortality was significantly related to proximity to heavily traveled roadways, particularly for those with high volumes of truck traffic. However, for the application of these studies to the 812 Analysis, one would also need the exposure distribution data for these source-specific surrogates, for the U.S., which are not readily available. Thus, it still is appropriate to make calculations based on PM2.5, rather than source-specific PM. It is important, however, to describe in a 'source chapter' what the most important sources are for PM. Specifically, it would be of interest to perhaps provide estimates of the contributions of various sources to the ambient PM, including both primary and secondary processes. The impact of a specific source may be larger or smaller its relative contribution to the ambient PM, as toxicities may be source dependent. This should also be discussed by the Agency .

The issue of a special role for traffic-related air pollution is complicated by the strong spatial gradient of primary pollutants from traffic sources. Studies around California freeways indicated that ultrafiine particle numbers can vary by an order of magnitude within100 meters, carbon monoxide and nitrogen oxides by somewhat smaller ratios, while $PM_{2.5}$ mass, which is dominated by regional background, shows little variation in proximity to traffic. Furthermore, the regional ozone is greatly reduced near the freeway due to its scavenging by nitric oxide. These spatial variations are important for some health effects and recent animal inhalation studies conducted at varying distances from a freeway show effects for close-in animals not seen for animals exposed at greater distances (Kleinman et al., 200x) and complement the observations of human populations in relation to roadway proximity (Hoek et al., 200x, OTHERS)

The cost-benefit analyses for 812 cannot address quantitatively this issue of traffic-pollutant-related effects because its grid-based exposure estimates are based on much larger spatial elements. The available database remains inadequate for the disaggregation of concentration-response relationships by pollutant source category. However, the HES recommends that the second prospective 812 analysis consider conducting some sensitivity analysis that incorporates the limited information on relative toxicities.

c. Extrapolation to Other Age Groups. For mortality, extrapolation of the C-R relationships to adult age-groups younger than those studied in the epidemiologic reports would be both uncertain and unnecessary. For chronic disease related endpoints, the baseline frequency increases rapidly with age and the public health impact for adult ages below 30 can be expected to be too small to significantly affect the totals obtained from the listed C-R functions.

The Subcommittee advises the Agency to consider broadening the mortality analysis for

all causes in infants. For health effects other than mortality, EPA should strongly consider broadening the age ranges beyond those included in the original studies that established the risk coefficients. In general, the age ranges studied were limited more by population access or study design considerations than by real restrictions on effects to the age group studied. Therefore,l the age range should be expanded where there is some reasonable physiological basis for expecting that the effects occur among a wider range of ages (e.g., applying CR functions to all children rather than just the ages of school children in the original study).

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d.. Exposure Assessment (Use of Grids): The exposure assessment approach utilizes the best available data and models. However, uncertainties remain large in this area – and the magnitude of these uncertainties will require better characterization in the second prospective analysis. Additional uncertainties arise in the translation of modeling results to population-relevant concentration estimates. In the case of ozone, the procedure involves modeling three multi-day episodes for the eastern US and two multi-day episodes in the western US. Each episode is approximately of one-two week's duration. These brief modeling results are then extrapolated to the entire ozone season by reference to observed data available from AIRS. The end result is a grid of 8x8 km hourly (ozone) or daily (PM) concentrations estimates that cover the continental US. EPA should work towards extending the modeling so that it covers longer, more representative periods of time, with less reliance on temporal extrapolation. Also there is a need to estimate uncertainties associated with this extrapolation.

The 8 km grid corresponds to the resolution at which population data (or estimates in the future) are available. Health impacts are then estimated by applying epidemiologically-derived C-R functions to the concentration, population, and baseline outcome rates for each grid. There is some question about the impacts of using these grid average concentration estimates as inputs to C-R functions which were derived from epidemiology studies in which a different sort or exposure measure is used (i.e., the concentrations at one or several population-oriented monitors) across a metropolitan area). There may not be a problem since both the pre- and post-control scenarios use the same (potentially biased) configuration. However, this should be discussed and verified. Center-city monitors may over-estimate population exposures in epidemiology studies whereas the gridded concentrations provide a broader, area-wide exposure estimate. The Subcommittee suggests that EPA do a sensitivity analysis in which the health assessment is repeated using the mean of urban monitor estimates instead of the grid estimate. This could be compared to the standard assessment results to see how big the differences are.

The Subcommittee also wishes to emphasize the need for efforts to improve exposure modeling and health assessment for people living near roadways and other local sources. A growing literature has emphasized the importance of roadway proximity as a risk factor for both elevated exposures and adverse health outcomes (Sioutas et al., recent southern cal study on elemental carbon and distance from roadways; **Brunekreef et al., Air Pollution from Truck Traffic and Lung Function in Children Living Near Motorways, (Epidemiology 1997; 8: 298-303);**oADD REFERENCE TO PREVIOUS COMMENT ON ROADWAY PROXIMITY

e. Infant effects . The Subcommittee proposes to include effects of air pollution on infant

mortality rates in the base estimates. In recent years, several international studies addressed the association of ambient air pollution and death during the first year of life. The outcome has also been included in the 2002 World Health Organization Global Burden of Disease study on ambient air (CITE). The WHO report relied on several time-series studies that relate daily exposures to PM to mortality for children under age five. The findings of effects of ambient air pollutants on respiratory inflammation in children support the evidence of effects on infants where respiratory infections are a major cause of infant deaths. The evidence for air pollutants to promote respiratory infections in infants has recently been corroborated (Belanger et al, AJE August 2003). A further argument to include infant mortality is the availability of effect estimates from a large U.S. cohort study conducted by Woodruff et al. It is based on ~4 million infants born 1989-91 in 86 metropolitan areas. Exposure was defined as the mean outdoor PM10 levels for the first two months of life. Woodruff controlled for some individual risk factors for infant mortality (i.e., maternal education, maternal ethnicity, parental marital status, maternal smoking during pregnancy) and other potential confounders (i.e., infants month and year of birth, average temperature during first 2 months of life), and found that postneonatal mortality from all causes (excluding violent death) increased by 4% (95% confidence interval [CI] 2-7%) for every 10 ¼g/m3 PM10. Sudden infant death syndrome (SIDS) and respiratory disease in infants with normal birth weight increased by 12% (95% CI 7-17%) and 20% (95% CI 6-36%) for every 10 ¼g/m3 PM10, respectively.

The Subcommittee also notes a re-analyses of Lipfert (CITATION?) that partly confirmed associations (for PM10 only). He used all U.S. infants born in 1990. However, exposure assignment was a larger non-systematic source of error in this study as the annual 1990 mean was assigned to each infant, thus, including pre- and post-mortem air quality data. The HES therefore recommends using the available studies to derive quantitative estimates of infant mortality.

Unfortunately, it is much more difficult to estimate the lost years of life associated with these deaths. In the most extreme case, each air pollution-related infant death loses the total years of life (life expectancy at birth). In the other extreme, one may hypothesize that all these infants were susceptible for infant death no matter what levels of air pollution they would experience in the first weeks of life (harvesting only). In the latter case, air pollution would be considered of limited public health relevance for this outcome. So far, no infant mortality study has formally addressed the issue of harvesting. Therefore, the person time lost among infants is not known. If harvesting was to explain the entire effects, these cases were of limited public health relevance. This range of uncertainty needs to be addressed as part of the uncertainty analysis.

The Subcommittee also notes that the reference to Kaiser et al. is misleading. Kaiser et al is not a study that investigates the association of air pollution with infant mortality. It is, however, a published abstract of an impact assessment that estimated the air pollution related burden of infant mortality, using the Woodruff et al. study as input information. A short paper is written on this, but it is still not published.

f. Asthma. The Subcommittee proposes to include asthma exacerbations for children and adults in the base case. The evidence for adverse effects of ambient air pollution, particularly PM and ozone, among asthmatics is sufficient to include it in the benefits analyses. On the other

hand, the association of new onset of asthma (incidence of doctor's diagnoses asthma) is currently less clear and probably a more complex issue of interacting environmental and genetic factors. Thus, the Subcommittee suggests not including it in the base case assessment at this time. The Subcommittee advises the Agency not to use the term chronic asthma. Asthma is, be definition, a chronic obstructive disease with the change the clinical level of obstruction a function of exposure to various triggers, including air pollution). New onset of asthma; incidence of physician-diagnosed asthma; prevalence of doctor's diagnosed asthma etc. are more appropriate terms.

The Subcommittee acknowledges that dealing with asthma exacerbations is a challenge in the context of benefits assessment for the 812 Analysis. The definition of an asthma exacerbation greatly various across studies, and is partly determined by study design. Panel studies are able to monitor daily onset of symptoms or medication use, whereas cross-sections or cohort studies usually ask about the occurrence or frequency of symptoms during the past year. Although all these approaches are useful avenues for epidemiological investigation, the methodological differences among studies make it difficult to apply their application for benefits assessments. The reasons are not primarily related to C-R functions but rather to the derivation of an appropriate background frequency of asthmatics, and the assignment of a monetary value. The latter may depend on the severity of an exacerbation. Neither asthma nor exacerbations are consistently defined in the air pollution studies. Nevertheless, the Subcommittee recommends that the Agency include asthma exacerbation in the base case and to rely on panel studies to derive a C-R function. In the selection of C-R function for asthma, the Subcommittee recommends selection of studies that have comparable design and baseline frequencies in both asthma prevalence and exacerbation rates. Among such a set of studies, C-R functions and background rates of exacerbations may be estimated (with distributions) for use in the 812 Analysis. The distribution of these parameters may be part of the uncertainty assessment. The original studies are a more appropriate source for these parameters given the uncertainty in its definition.

Exhibit D-7 in the draft analytical plan lists the candidate studies considered by EPA. All except the two McConnell and the Pope et al (1991) papers are based on comparable approaches. Ostro et al, 1991 did not publish the baseline frequency of the exacerbation outcome (or the EPA document did not list it), thus, it is difficult to judge the comparability of this study. The remaining exacerbation studies indicate rather similar definition of outcomes, i.e., the baseline frequency of the exacerbation (and the prevalence of asthmatics) are sufficiently similar (0.04-0.08 event per day) with the exception of Yu et al, whose outcome was extremely frequent (0.6 per person-day). Thus, it appears to be appropriate to only pool the studies listed as # 2-4 () and 7-8 () and ignore the others for the quantitative approach. The HES recommends that the Agency generalize the effects to the age group 6-18 as well as adults (>18). *NB: If the estimates are extrapolated over a wider age range, than national estiames of incidence need to be used since they are very age-dependent*. The exclusion of young children is based on the uncertainty in the definition of asthma in early life and the exacerbation thereof.

One may assume that, among asthmatics, a day with an exacerbation may be a day of restricted activity. Thus, the benefit derived for restricted activity days may partly or fully include the asthma exacerbations. This has to be considered in the total assessment.

In the absence of independent response functions for PM and ozone, the Subcommittee recommends the Agency use only one pollutant as a surrogate for the whole effect, although this may underestimate the overall effect on asthmatics. *This is different that what we recommended for mortality -- !?!?!?*

The 812 report should mention that the social costs of asthma are most likely underestimated since the epidemiological studies do not incorporate the treatment and averting behavior asthmatics may engage in to mitigate the adverse effects of air pollution.

g. Effects of Sulfur Dioxide (SO_2), Nitrogen Dioxide (NO_2), Carbon Monoxide (CO) (SONOCO Suite). As outlined in Exhibit 6-1 in the Analytical Plan, a few selected endpoints for the SONOCO suite will be quantified and monetized, and a few have been selected for alternative or sensitivity analyses. The HES concurs with the use of the C-R functions as used in the 1st Prospective study as the best available estimates since little, if any, new work has been reported and with the plan to update these functions as new information becomes available during the 812 process. In supporting the quantification of some endpoints in relation to the SONOCO gases, the HES is not taking a view on causality or biological plausibility of these specific pollutants. Rather, the Subcommittee is assuming that, where they are used, C-R functions in these pollutants are quantifying adverse effects of some aspects of the pollution mixture which are not already taken into account via C-R functions in PM or ozone. Where C-R functions are used for each of the three gases, e.g. for respiratory hospital admissions, the HES asks that the possibility of double-counting be considered and discussed, when aggregating across all pollutants quantified.

The HES advises that the Agency provide an expanded discussion of the following points on the Analysis. In regard to SO_2, the HES notes that Pope et al. (2002) show mortality associations for sulfur oxides, albeit there are also associations between SO2 and non-cardiopulmonary deaths as well. The HES advises that the Agency discuss the pros and cons of possible inclusion of sulfur dioxide and mortality from longer-term exposure. In regard to nitrogen dioxide, European short-term effect studies suggest an interaction with PM (i.e., PM effects are increased in the presence of NO_2 and NO_2 is significantly associated with increased respiratory infections). It is not clear whether or not these will be included in the analysis. Interaction between pollutants is not discussed (i.e., ozone and NO_2 have more than additive effects in toxicological studies). Finally, in regard to CO, the Subcommittee asks the Agency to consider and discuss whether non-asthma ER visits for respiratory or cardiovascular causes should be moved to the base case analysis.

Agency Charge Question 12: New and Revised Endpoints for Particulate Matter and Ozone

Charge Question 12. EPA seeks advice from the Council regarding the technical and scientific merits of incorporating several new or revised endpoint treatments in the current analysis. These health effect endpoints include:

a. Premature mortality from particulate matter in adults 30 and over, PM (Krewski et al., 2000);

b. A PM premature mortality supplemental calculation for adults 30 and over using the Pope 2002 ACS follow-up study with regional controls;
c. Hospital admissions for all cardiovascular causes in adults 20-64, PM (Moolgavkar et al., 2000);
d. ER visits for asthma in children 0-18, PM (Norris et al., 1999);
e. Non-fatal heart attacks, adults over 30, PM (Peters et al., 2001);
f. School loss days, Ozone (Gilliland et al., 2001; Chen et al., 2000);
g. Hospital admissions for all respiratory causes in children under 2, Ozone (Burnett et al., 2001); and,
h. Revised sources for concentration-response functions for hospital admission for pneumonia, COPD, and total cardiovascular: Samet et al., 2000 (a PM10 study), to Lippmann et al., 2000 and Moolgavkar, 2000 (PM2.5 studies).

HES Response: The HES comments regarding new endpoints used for particulate matter and ozone appear immediately below in separate sections

a. New and Revised Endpoints for Particulate Matter. The HES generally supports the incorporation of the new and revised endpoints as indicated in charge questions 12. However, some modifications are suggested, specifically:

1. The Pope et al., 2002 should be used for the base estimate of premature mortality, rather than the Krewski et al., 2000. As indicated below, this data set adds nine years of data to the follow-up period, and additional exposure data. The authors are basically the same as in the original study using the ACS and in the Krewski et al. 2000 study so they benefit from the insight gained by the Krewski reanalysis. Sensitivity analysis for this endpoint could use other estimates from Pope et al. (2002), Krewski et al., 2000 and/or the results of Dockery et al., 1993. Whichever is used, the choice should be explained in the document.

2. Estimates for hospital admissions studies (c and h) should utilize the large number of studies relating PM10 to both respiratory and cardiovascular admissions rather than simply rely on the Moolgavkar et al., 2000 and the Lippmann et al. 2000 of PM2.5. Estimates should be based on a meta-analysis of these studies conducted in multiple cites throughout the U.S. As such, they represent a broader range of conditions, co-pollutants, and climates than does reliance on any single study. In addition, the studies using PM10 incorporate the potential effects of coarse, as well as fine, particles.

3. As discussed above in Charge Question 11, several other endpoints should be added to the base case analysis including: (1) asthma exacerbations and PM10; and (2) infant mortality and PM10 so that the base case will be more reflective of the comprehensive scientific analysis of health benefits that the Clean Air Act requires. In addition, as indicated above, the HES recommends that the age categories for the applied effects be increased when it is reasonable.

The Subcommittee also notes that EPA has 5 criteria to select C-R functions (page 6-10,

top). The HES requests EPA to provide more explanation of how criterion 5 (biological plausibility) was applied

.

b. New and Revised Ozone Endpoints. The Subcommittee concurs with EPA's two new endpoints related to ozone exposure. Gilliland et al. 2001 demonstrated acute associations between increased illness-related school absences among children enrolled in the California Children's Health Study. The study methods were thorough in terms of population characterization, exposure assessment and outcome assessment. Respiratory hospital admissions for children under 2 years of age in relation to short-term ozone exposures is supported by Burnett et al., 2001.

Agency Charge Question 13 Baseline Data

Agency Charge Question 13: EPA seeks advice from the Council regarding the merits of applying updated data for baseline health effect incidences, prevalence rates, and other population characteristics as described in chapter 6. These updated incidence/prevalence data include:

a. Updated county-level mortality rates (all-cause, non-accidental, cardiopulmonary, lung cancer, COPD) from 1994-1996 to 1996-1998 using the CDC Wonder Database;
b. Updated hospitalization rates from 1994 to 1999 and switched from national rates to regional rates using 1999 National Hospital Discharge Survey results;
c. Developed regional emergency room visit rates using results of the 2000 National Hospital Ambulatory Medical Care Survey;
d. Updated prevalence of asthma and chronic bronchitis to 1999 using results of the National Health Interview Survey (HIS), as reported by the American Lung Association (ALA), 2002;
e. Developed non-fatal heart attack incidence rates based on National Hospital Discharge Survey results;
f. Updated the national acute bronchitis incidence rate using HIS data as reported in ALA, 2002, Table 11;
g. Updated the work loss days rate using the 1996 HIS data, as reported in Adams, et al. 1999, Table 41;
h. Developed school absence rates using data from the National Center for Education Statistics and the 1996 HIS, as reported in Adams, et al., 1999, Table 46.
1. Developed baseline incidence rates for respiratory symptoms in asthmatics, based on epidemiological studies (Ostro et al. 2001; Vedal et al. 1998; Yu et al; 2000; McConnell et al., 1999; Pope et al., 1991).

HES Response: Overall, the Subcommittee commends the EPA for its efforts to identify appropriate databases to update and strengthen population characteristics and health outcome rates. There are some issues, however, that remain with the data sources and the use of the data that need to be considered in further detail before the plan is implemented. The HES highlights the major issues in comments here.

Fundamentally, baseline incidence rates are multipliers in the estimation of some health effects and therefore have a direct influence on the estimation of effects and potential benefits. In the first prospective analysis, preference was given to baseline incidence data at the county level, followed by national-level data. If those were not available, baseline incidence data for the study population were used to derive the impact functions. The primary data sources were the 1990 U.S. Vital Statistics and the 1997 National Hospital Discharge Survey (NHDS) of the Centers for Disease Control and Prevention. For the second prospective analysis, the baseline incidences will be adapted to match the specific populations studied and additional sources of information at the regional level are included for hospitalization rates and emergency room visits. These additions can be of some help in improving the accuracy of benefits calculations by location.

However, there are several factors that can alter the incidence rates as they are projected over time. One such issue involves multiple age groups. For example, the draft plan states that the baseline incidence rates for older populations are higher than the rates for younger populations. This statement relies on the assumption that the population age distribution will tend toward older ages over time. The demographic shift coupled with increased susceptibility for older individuals could lead to increased baseline incidence rates. The HES notes that on page 6-15 of the Analytical Plan, paragraph 1, line 6 the Agency states, "baseline incidence rates…may decline slightly over time," but there is no justification for this statement. This seems to contradict what was said earlier and leads to an assumption of uncertainty that may be unwarranted.

Although EPA states, "we will not attempt to estimate changes in baseline incidence rates," perhaps an analysis of rate trends retrospectively to 1990 or earlier could be useful in ascertaining how such changes contribute to overall uncertainty. EPA should evaluate whether there may be useful contrasts between the incidence rates used in the first analysis and the updated incidence rates that could shed some light on this issue.

While many of the data sources selected for the second prospective analysis are appropriate, some may need to be considered more thoroughly to appreciate their specific limitations before use in the cost-benefit analysis. The following themes emerged from the HES review of these data sources and exemplify the types of issues that need to be evaluated as EPA develops its analytic plans.

a. The number of persons or health events included in some of the national surveys may not be very large, particularly at the county level targeted in portions of draft. For example, EPA's plan to work with more than one year of the CDC Wonder data will help address this problem for many outcomes, but "missing" data will probably remain for several of the outcomes. This situation raises the question as to whether the use of particular health events may introduce a highlevel of uncertainty into the analysis. At the present time, the plan does not recognize this problem, discuss what level of "missing" data would be judged as unacceptable, or explain what alternative outcome categories or data sources would be used. The Subcommittee advises the Agency to distinguish between (i) the spatial level on which the analysis is conducted, e.g. 8x8km grid cells and (ii) the spatial level at

which results will be reported and conclusions will be drawn. It is likely that results for small areas will be (much) less reliable than for bigger ones, because often the small area input data will be average values from wider geographical regions, applied to all small areas of that region.

b. Selecting specific diagnostic codes within broad health outcome categories, as planned, are expected to provide health outcome estimates that more closely link to the results of epidemiological studies. However, if in these efforts to achieve a match, the outcome specification is too narrow (e.g., "acute bronchitis" instead of "all respiratory conditions"), small numbers will seriously reduce the reliability of the analysis. Therefore, careful consideration of the diagnostic codes to use with the related tradeoffs in uncertainty will be an important step in constructing the baseline datasets. (ISSUE FROM FINTAN: Should this then push us towards 'all respiratory hospital admissions', rather than have separate functions for COPD and pneumonia?)

c. Additionally, there is concern that reliance on poorly defined diagnostic categories will result in estimates with a high degree of error. Examples of such categories or diagnoses include acute and chronic bronchitis, asthma exacerbation, school absence, etc. In these cases, the national dataset definitions should be compared to the definitions used in epidemiological studies and a determination made as to whether the national sources will provide comparable outcome data. If the definitional differences are large, it may be more prudent to use the epidemiological studies to construct baseline rates, depending in part on the size of the baseline epidemiological studies and the representativeness of their populations.

d. The design of the national data bases relies on complex sampling schemes that may or may not include sizable populations at risk for air pollution-related health effects. For example, the NHDS and the National Hospital Ambulatory Medical Care Survey (NHAMCS) use sampling designs that exclude specific types of hospitals and, as a result, exclude potentially sizable segments of the U.S. population (e.g., military and institutionalized persons). These groups may be at increased risk for important adverse outcomes of interest (e.g., heart attacks, chronic bronchitis, cancers, etc), which would then be undercounted by relying solely on the identified national data sets. Omitting these groups would bias the prevalence downwards and result in lower effect estimates. For outcomes where the exclusions may result in significant underestimates, careful consideration should be given to identifying additional data sources (e.g., databases for institutionalized persons, or the health care databases of the U.S. Department of Defense and/or Veterans Affairs) for otherwise excluded populations. Additionally, the HES recommends that EPA seek expert consultation from the National Center for Health Statistics (NCHS) for in depth information about the design of the selected databases and the limitations that need to be considered when applying the data for EPA's estimation purposes. The Center's experts can

be reached through www.cdc.gov/nchs/ or 301-458-4636.

e. The use of 1999 data from the National Health Interview Survey (NHIS) may present problems in the analysis. Despite the strength of having supplemental data on asthma outcomes, the 1999 survey relies on an unusually small sample size. This important limitation will probably result in "missing" data especially for county-level purposes. Whether the sample is so small that it will result in unreliable rates and thereby prevent the use of this year of data or whether its use only for specific analyses may be appropriate needs to be determined. If this year of data turns out to be unacceptable, the use of a more recent year with a larger sample size is recommended. The data may be sufficient for national or state-wide conclusions, but not for small-area conclusions. The Subcommittee asks EPA to consider the extent to which the analysis will be (i) reported and (ii) interpreted at small-area level.

f. The methods planned to construct the work loss and school absence rates are not clear in the documentation reviewed by the HES. For example, it is not clear which health condition(s) on the cited Tables 41 and 46 will be used or what level of relative standard errors will be judged as acceptable for estimation purposes. Additionally, which National Center for Education Statistics (U.S. Dept. of Education) data will be used in combination with which NHIS data is not clear.

g. The epidemiological studies listed for developing the pediatric asthma symptom rates as a group provide good evidence. However, these studies depend on self-reported outcome data with little or no assessment of the reliability of the data; EPA should explore this issue with the authors. HOW? The HES also noted that all of these papers studied populations living in the western United States. This observation raised the question as to whether the air pollution mix and/or the characteristics of the populations studied need be evaluated to determine how relevant the results are for the entire U.S. population. If application of these epidemiological data to the U.S. population would introduce important uncertainties, then appropriate adjustments to reduce those uncertainties need to be identified. Application of these epidemiological data to the entire country may introduce additional uncertainty

Agency Charge Question 14. Scientific merits of alternative methods to expert elicitation for estimating the incidences of PM-related premature mortality

Charge Question 14. EPA plans to initiate an expert elicitation process to develop a probability-based method for estimating changes in incidence of PM-related premature mortality. Plans for this expert elicitation are described in chapter 9 of this blueprint, and a separate charge question below requests advice from the Council pertaining to the merits of the design of this expert elicitation. EPA recognizes, however, the possibility that this expert elicitation process may not be fully successful and/or may not be completed in time to support the current 812 analysis. Therefore, in order to facilitate effective planning and execution of the early analytical

steps which provide inputs to the concentration-response calculations, EPA seeks advice from the Council regarding the scientific merits of alternative methods for estimating the incidences of PM-related premature mortality, including advice pertaining to the most scientifically defensible choices for the following specific factors:

a. Use of cohort mortality studies, daily mortality studies, or some combination of the two types of studies
b. Selection of specific studies for estimating long-term and/or short-term mortality effects
c. Methods for addressing –either quantitatively or qualitatively– uncertain factors associated with the relevant concentration-response function(s), including
i. Shape of the PM mortality C-R function (e.g., existence of a threshold),
ii. PM causality,
iii. PM component relative toxicity, and
iv. PM mortality effect cessation lag structure
v. Cause of death and underlying health conditions for individuals dying prematurely due to chronic and/or short term exposures to particulate matter
vi. The use of ambient measures of exposure for estimating chronic health effects, given recent research reviewed in the NAS (2002) report that questions the implications of using ambient measures in cohort studies

HES Response: The Subcommittee notes that there is some overlap between this charge question and charge questions 16,17 and 29. HES recommendations regarding C-R functions for PM also affect recommendations on expert elicitation and alternatives to expert elicitation. Those recommendations will be discussed in response to charge question 29. The response to charge question 16 will address the cessation lag issue and the response to charge question 17 will address the question of alternative estimates

The Subcommittee agrees with EPA's current proposal to use cohort based estimates in the Base Case. Different cohort studies and, within each study, various C-R functions are available, using different causes of death, exposure windows, subgroups, and models. The HES concludes that the Base Case should use the Pope et al. 2002 study, which relies on a larger number of death and longer follow-up of the American Cancer Society (ACS) cohort than does Pope et al. (1995) or its HEI reanalysis (Krewski et al., 2000).. In addition, this analysis profited from the extensive experience and review process of Krewski et al. 2001, two of whose key authors (Krewski, Burnett) are also co-authors of Pope et al., 2002. The HES proposes to use total mortality estimates. The cause specific estimates can be used to communicate the relative contribution of the main air pollution related causes of death. It is, however, not recommended to primarily use cause-specific estimates given the larger uncertainties in these estimates; these originate from the smaller number of cases and potential errors in coding of causes of death.

In the Analytical Plan, EPA makes good arguments for the use of the ACS cohort for the Base Case. However, the HES recommends modification in the way ACS and the Harvard 6-Cities Studies are compared (e.g., in Appendix D). ACS has some inherent deficiencies, in particular the imprecise exposure data, and the non-representative (albeit very large) population.

Thus, ACS is not 'the better study', but, at this point in time, a good choice for a prudent RIA. The Harvard 6-Cities C-R functions are valid estimates on a more representative although geographically selected population, and its updated analysis has not yet been published. The Six Cities estimates may be used in a sensitivity analysis to demonstrate that with different but similarly plausible selection criteria for C-R functions' benefits may be considerably larger than suggested by the ACS study. The not yet published updated estimates of the expanded Harvard follow-up will be particularly useful for this purpose when they are accepted for publication in a peer-reviewed journal.
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The Subcommittee had several discussions about the use of time-series based effect functions. In line with published work on this issue, the HES would like to emphasize the importance to understand and communicate the fundamental differences in the outcome of these studies as compared to cohort studies.

To estimate the full range of the contribution of air pollution to all processes that ultimately contribute to shortening in life expectancy one needs to follow large cohorts over many years to measure the association of the exposure experience with the person time in the population. ACS is an example of this approach. Although ACS published the data in the 'case domain' (body counts), the underlying model uses person-year information (or survival time).

Time series studies, on the other hand,estimate specifically the number of premature death affected by the exposure conditions shortly before death. The approach counts death rather than to measure person-time, thus, it does not provide direct information about the lost time of life among these death. The Subcommittee therefore reminds the Agencies that any assumption about the amount of time lost among these acute effect cases is a matter of judgment. The only information that can be derived from the literature is the evidence that the lost time appears to be rather short (harvesting) among only a small fraction only.

Although cohort studies can be considered to measure the full range of person-time lost due to all kinds of effects of air pollution, this assumption is only theoretically true. Due to methodological limitations, the currently available cohort studies may most likely miss part of the time lost or the attributable cases (Kunzli, Medina et al., 2001; Martuzzi, 2001). The very rough estimates of long-term exposure used in these studies are unlikely to capture the mortality effects of specific short-term exposure patterns or the long term mortality consequences of exposures in early life time (let's discuss these two cases), which have been shown to affect pulmonary development. In addition, deaths that lose only a short period of time are not likely to to be fully captured in these studies . Thus it is conceivable that the total air pollution related death toll may be the sum of the cases derived from cohort studies plus some unknown fraction of those cases derived from time-series estimates plus cases missed from both (i.e., from early exposure??). The overlap in these two quantities is not known. In the prudent Base Case, the HES proposes that EPA assume full overlap, i.e. to ignore the additional short-term cases in the benefit analysis. In the sensitivity analysis or the expert elicitation, other probabilities of the overlap could be considered. (NB: but if rank order of cities relatively unchanged over time and no migration, early childhood exposure probably reflected in cohort estimates???)

The Subcommittee emphasizes that the evidence of effects of long-term or life-time exposure on chronic processes leading to premature death should not only be discussed in the context of the few cohort studies or the case-control study published for lung cancer (unclear) (Nyberg, Gustavsson et al. 2000). The HES emphasizes that studies showing impaired lung function growth and accelerated decline in areas with higher pollution strongly support the notion of chronic effects. Lung function is one of the strongest long-term predictor of life expectancy, thus, the findings on reduced lung function in children and adult are consistent with the shorter life expectancies as observed in the cohort studies. Scenarios of benefit estimates that entirely ignore cohort based C-R functions are therefore inappropriate.

The attempt to combine cohort estimates with some fraction of the time-series based cases requires that C-R functions have to be selected from time-series studies. The Subcommittee recommends using estimates for total mortality that take into account the possibility of some time delay between the air pollution related trigger of a terminal phase and the occurrence of death. Time-series studies with distributed lag models take this possibility into account and, thus, provide the C-R functions of choice to characterize the full range of short-term effects. It is also preferred to use estimates that are not subject to the statistical GAM problems (Dominici, McDermott et al. 2003, or those summarized in the fourth draft (June 2003) of the Agency's Criteria Document for PM)

The Subcommittee agrees that the interpretation of mortality risk results is enhanced if estimates of lost life years can be made. As mentioned, in contrast, time series studies do not provide direct estimates of the time lost. (what about paper by Burnett et al. 2003 EHP?) Therefore, time lost among these acute cases cannot be readily derived and any assumptions on the average time lost remain a matter of judgment. The time lost may depend on the cause of death and the age at death. For example, whereas the acute terminal effects of air pollution on patients with lung cancer may make only a small change on life expectancy, a myocardial infarction in a 60 year old may lead to many years of life lost.

Different methods are available to estimate time lost among cohort based cases of death. The Subcommittee proposes that EPA use life table approaches such as the one describe by Miller et al. (2 refs?) Both apply estimates of relative risk to a given underlying population-at-risk and its associated age-specific death rates. The 'static' approach ignores how different death rates in any one year alter the population-at-risk in future years. Treating years as independent, it provides estimates of 'extra deaths' or 'lives saved' each year. It seems that this is what EPA proposes. The 'dynamic' approach uses life-table methods to follow over time the impact on the population-at-risk of higher (lower) age-specific death rates. The consequent changes to the population-at-risk affect mortality estimates. These estimates are most naturally expressed in terms of earlier (later) deaths, i.e. in terms of changes in life expectancy or life-years lost (LYL). Results can be expressed in terms of 'extra' deaths or 'saved' lives in various time-periods.

Which approach to use depends on (i) correctness; (ii) workability; and (iii) whether the differences matter. On (i), the dynamic approach is more comprehensive, more correct, and pushes for greater transparency of assumptions. On (ii), the static approach is easier to implement. However, the technical implementation issues of the life table approach are not difficult in principle and have been solved in practice. They need not be a deterrent to implementation. Workability also requires suitable economic valuation of an 'extra' death or LYL, respectively. On (iii), the two approaches give the same results for year 1. They diverge increasingly with time. This divergence, and its impact on mortality, are positively associated with the size of the differences in hazard rates. The importance of the differences in mortality impacts is negatively associated with the discount rate used.

The Subcommittee recommend that (a) whichever approach is used as primary, the other is used as sensitivity, and the results compared; (b) if differences are non-trivial, then the dynamic (life-table) approach be taken as best (Miller and Hurley 2003)

The Subcommittee also agreed that the whole range of uncertainties such as the questions of causality, shape of C-R functions and thresholds, relative toxicity, years of life lost, cessation lag structure, cause of death, biologic pathways, or susceptibilities may be viewed differently for acute effects versus long-term effects. Thus, expert elicitation and the incorporation of uncertainties need to be considered separately for cohort and time-series based procedures. I don't think we addressed the issues of 14.c.i, ii, iii, and vi dealing with threshold, causality, relative toxicity, and uncertainty related to exposure measures

Agency Charge Question 15: Alternative Analysis for PM Control

Charge Question 15. EPA estimates of benefit from particulate control may underestimate the impact of nonfatal cardiopulmonary events on premature mortality and life expectancy. For the base analyses, which rely on cohort evidence, the limited follow-up periods for the cohorts may not fully capture the impacts of nonfatal cardiovascular events on premature mortality later in life. For the alternative analyses –including cost-effectiveness analyses– which rely more on acute studies and life-expectancy loss, the years of life are estimated only for fatal events. Yet nonfatal events such as myocardial infarction reduce a person's life expectancy by a substantial percentage.

a. Do you agree that EPA, in the 812 analyses, should adjust benefit estimates to account for the mortality effects of non-fatal cardiovascular and respiratory events?
b. What medical studies and mathematical models of disease might be useful to review or use if EPA moves in this direction?
c. When the nonfatal events are valued in economic terms, should EPA assume that the published unit values for morbidity already account for the life-expectancy loss

or should an explicit effort be made to monetize the resulting longevity losses?

HES Response: In regard to Question15.a., a reasonable presumption to make is that the cohort mortality studies capture the full effect of PM on mortality and it would not be appropriate to add additional mortality effects that might be associated with quantified PM morbidity effects such as nonfatal heart attack or chronic bronchitis. As noted above (see response Charge Question 14), some effects may be omitted in the cohort results. These omissions might be for those for individuals with very short life expectancy (very short-term shift in timing of death), or those associated with very long term or distant past exposures (beyond the time frame of the cohort or due to increased measurement error from cohort member migration). ???again issue of what is picked up in cohort?

If short-term exposure mortality studies were to be used as the basis of mortality estimates *and* if the cohort study estimates were being ignored,then it would be appropriate to add mortality effects of PM-induced chronic illnesses. However, in response to charge question 14 above, the HES has strongly advised against ignoring the cohort study estimates.

The HES also discussed Quality Adjusted Life Year (QALY) estimates for cohort study based mortality. The question is how the morbidity period that precedes death might be considered. The cohort study results do not tell us to what extent PM causes the ongoing disease that ultimately leads to death versus aggravating an already existing disease, but the HES sees from the morbidity studies that PM is a risk factor for onset of new chronic disease, at least for chronic bronchitis. Models of disease, as discussed for question 15.b. might be helpful in determining how to consider this. For some (uncertain) share of the deaths, PM is likely causing the disease as well as the death.

In regard to question 15.b., the HES notes (i) that this is a conditional question (what medical studies and mathematical models of disease might be useful to review or use if EPA moves in this direction – emphasis added) and (ii) that, with use of the cohort studies, it is not necessary to move in this direction. Nevertheless, it is useful to consider the issue. The ideal basis for such estimates would be fully validated quantitative causal models of chronic cardiovascular and respiratory diseases, including contributions of air pollutants to both the chronic underlying disease processes, and acute events that precipitate clinical manifestations such as myocardial infarctions and arrhythmias associated with “sudden death”. This ideal is not yet close to being realized. However there are some data and models that can contribute to the construction of reasonable preliminary assessments.

Some models can take the form of analogies with the prevention of fatal and nonfatal cardiovascular events by other types of interventions—for example pharmacological interventions such as cholesterol-lowering drugs. Long term double-blind intervention studies done for testing the efficacy and safety of these agents are the most secure basis for determining health improvements that are causally related to specific risk-factor-related interventions, although in some cases the length of follow-up may not be sufficient to provide ideal full-lifetime evaluations.

Longer follow-up is almost certainly possible by the use of long term prospective epidemiological observations of the relationships between specific cardiovascular risk factors (e.g., fibrinogen levels, low FEV1 levels, low heart rate variability) and both total mortality and nonfatal cardiovascular and respiratory disease events. Such analogies may be considered promising as each of these three biomarkers has both associations with ambient airborne particle levels (Ackerman-Liebrich et al., 1997; Schwartz, 2001; Xu et al., 1991; Chestnut et al., 1991; Pope et al., 1999; Gold et al., 2000) and significant independently predictive associations with cardiovascular mortality (Knuiman et al., 1999; James et al., 1999; Ryan et al., 1999; Lang et al., 1990; Folsom et al., 1997; Danesh et al., 1998; Huikuri et al., 1998; Tsuji et al., 1994; Klieger et al., 1987). To do these calculations, the long term prospective cardiovascular epidemiology observations would be used to construct life table models to indicate the long term changes in both non-fatal and fatal cardiovascular and respiratory events that would be associated with specific amounts of change in each biomarker across the range of age groups where this has been studied. From these analogies, the amount of life shortening falling outside the follow-up limits of the air pollution cohort studies could be estimated

In the Global Burden of Disease report (cite), WHO utilized other techniques for estimating effects of chronic exposure prior to mortality. Therefore, HES also recommends that these methods by investigated.

In regard to question 15.c., "Do unit values for morbidity reflect life expectancy loss?", this will be further discussed with the Council, but in general it depends on how the value estimate was derived. Cost of illness estimates include life expectancy losses (which are valued based on lost earnings/productivity) only if they are explicitly added. The values EPA is currently using for hospital admissions and for non-fatal heart attack do not include anything for life expectancy losses. Values based on stated preference studies can be assumed to include life expectancy losses only if respondents are told that these are a component of the health effect being valued or if it is commonly understood that there is an elevated risk of death associated with the illness (as might reasonably be assumed for cancer, for example). This para unclear and maybe unwarranted since we say that impacts of these health effects should be included in cohort studies so no need to add more valuation, except for “pain and suffering” which is always omitted.

Regarding the second part of Charge Question 15c (should an explicit effort be made to monetize the resulting longevity losses): Actual longevity losses from chronic disease will be picked up by the cohort studies. If, as the HES advises, the cohort study estimates are always included, then it would not be right to incorporate the longevity losses also in the valuation of chronic disease. EPA might consider whether the fear of earlier death is included appropriately, as part of reduced life quality, in the valuation of chronic disease.

Agency Charge Question 16. Cessation Lag

Charge Question 16. In recent EPA rulemakings, EPA's "base estimate" of benefit from PM control has been based on cohort epidemiological studies that characterize the chronic effects of pollution exposure on premature death as well as capturing a fraction of acute premature

mortality effects. If these chronic effects occur only after repeated, long-term exposures, there could be a substantial latency period and associated cessation lag. As such, a proper benefits analysis must consider any time delay between reductions in exposure and reductions in mortality rates. For the acute effects, such as those considered in EPA's alternative benefit analyses, the delays between elevated exposure and death are short (less than two months), and thus time-preference adjustments are not necessary.

a. In the previous 812 analysis and in recent rulemakings, EPA assumed a weighted 5-year time course of benefits in which 25% of the PM-related mortality benefits were assumed to occur in the first and second year, and 16.7% were assumed to occur in each of the remaining 3 years. Although this procedure was endorsed by SAB, the recent NAS report (2002) found "little justification" for a 5-year time course and recommended that a range of assumptions be made with associated probabilities for their plausibility. Do you agree with the NAS report that EPA should no longer use the deterministic, 5-year time course?

b. One alternative EPA is considering is to use a range of lag structures from 0 to 20-30 years, with the latter mentioned by NAS in reference to the Nyberg et al PM lung cancer study, with 10 or 15 years selected as the mid-point value until more definitive information becomes available. If this simple approach is used, should it be applied to the entire mortality association characterized in the cohort studies, or only to the difference between the larger mortality effect characterized in the cohort studies and the somewhat smaller effect found in the time series studies of acute exposure? Should judgmental probabilities be applied to different lags, as suggested by NAS?

c. Another option under consideration is to construct a 3-parameter Weibull probability distribution for the population mean duration of the PM mortality cessation lag. The Weibull distribution is commonly used to represent probabilities based on expert judgment, with the 3-parameter version allowing the shaping of the probability density function to match expected low, most likely, and expected high values. EPA is still considering appropriate values for the low, most likely, and expected high values –and therefore for the Weibull shape and location parameters– and EPA is interested in any advice the Council wishes to provide pertaining to the merits of this approach and/or reasonable values for the probability distribution.

HES Response: Given the purpose of the 812 studies (to estimate a future situation), the time/lag is a very important issue. As noted by EPA, for short-term effects (including time-series based observations of mortality) this is not a problem, and there is even published evidence that these short-term effects closely follow changes in the pollution, thus, benefits are 'immediate' (on the annual aggregate level). For long-term effects, HES noted that empirical evidence is lacking to directly inform the choice of the lag distribution. This is because the cohort mortality studies reported to-date have lacked data on the long term time-course of exposures for each cohort member; such data if available might enable testing hypotheses regarding alternative exposure lag structures, if sufficient statistical power was

available. Lacking direct information from the cohort studies themselves, new insights regarding the shape of the cessation lag can only come from improved mechanistic understanding of the chronic mortality exposure-response relationship. Information that may prove valuable in this regard could include results from clinical, experimental animal, and in-vitro studies, and analogies with the health effects of other long-term inhalation exposures, such as cigarette smoking. The clinical intervention literature (e.g., cardiovascular trials) or smoking cessation data may be useful.

It is recommended to derive models for each cause of death considered in the RIA as the lag structure most likely differs for different health problems. As a general rule, one may assume that the longer the air pollution sustained disease process is, the longer the delay. For example, if inhalation of carcinogens from ambient air contribute to the incidence of lung cancer, the pathophysiologic process between exposure and death may take many years (for the average case) and the benefit of a 2000 to 2010 reduction in carcinogenic constituents in PM may lead to a reduction in lung cancer rates only after many years. For effects of long-term PM exposures on pulmonary disease (e.g., COPD), a useful model may be the change in the natural history of lung function with exposure to air pollution. Several studies are showing effects of long-term PM exposures on decreased lung function (Children's Health Study; Yale ISEE abstract 2002). By analogy with cigarette smoking, this may put people on steeper trajectories of lung function decline, which is a known risk factor for premature mortality (cite needed). This might imply distributed lags extending over a substantial fraction of a lifetime. On the other extreme, some cardiovascular deaths captured in the cohort studies may be due to air pollution during the last months to years prior to death whereas the underlying susceptibility to a cardiovascular death may be due to non-air pollution causes (e.g. diabetes). Life time lost, captured in the cohort, may still be rather long (see above comments 14 a and 15), e.g years. Clean air policies would bring a rather immediate benefit for such kind of cases. Finally, to the extent that cohort results capture a portion of the acute time-series mortality effects of PM, there may be an even shorter distributed lag. What about CV deaths? For example, Glantz (cite) indicates that improvements to heart disease occur within one to three years….Need to check this.

Several alternatives lag structures have been presented by EPA staff, including the use of a flexible Weibull distribution spanning ars up to 25 years. It would be useful to utilize a distribution which could incorporate time lag to benefits based on three different patterns: purely acute effects based on exposure of 0-6 months, short-term cohort based on exposure of 2-5 years, and long-term cohort effects extending out 15-25 years. Thus, the HES supports either the use of a Weibull distribution or a simpler distributional form, such as uniform (made up of three segments to cover the three exposures periods outlined above), given our lack of knowledge on the form of the distributions. An important question to be resolved is what the relative magnitudes of these three components should be, and how much of the acute effects are assumed to be included in the cohort effect estimate. The Subcommittee suggests that if the three-segment uniform distribution is used, a smoother might be applied to the lag function to smooth the

discontinuities. Given the current lack of direct data upon which to specify the lag function, HES recommends that this question be considered for inclusion in future expert elicitation efforts and/or sensitivity analyses. As noted, time lag to benefits may depend on the cause of death and the underlying morbidity processes that ultimately lead to premature death.

Agency Charge Question 17. Alternatives to the Base Estimate

Charge Question 17. In support of Clear Skies and several recent rule makings the Agency has presented an Alternative Estimate of benefits as well as the Base Estimate. EPA developed the Alternative Estimate as an interim approach until the Agency completes a formal probabilistic analysis of benefits. NAS (2002) reinforced the need for a probabilistic analysis. The Alternative Estimate is not intended as a substitute method and needs to be considered in conjunction with the Base Estimate. Presentation of Base and Alternative estimates in the 812 Report may not be necessary if the probability analysis planned for the 812 Report is successful. While the Base Estimate assumes that acute and chronic mortality effects are causally related to pollution exposure, the Alternative Estimate assumes only acute effects occur or that any chronic effects are smaller in size than assumed in the Base Estimate. The Council's advice is sought on the following matters:

a. It has been noted by some particle scientists that the size of estimates based on time series studies that incorporate a distributed lag model, accounting for effects of 30 to 60 days after elevated exposure, may be similar in size to some interpretations of the results from the cohort studies. Does the Council agree that it is a reasonable alternative to use an estimate of the concentration-response function consistent with this view? If the Council agrees with the assumption, can it suggest an improved approach for use in an Alternative Estimate? The agency also seeks advice on appropriate bounds for a sensitivity analysis of the mortality estimate to be used in support of the Alternative Estimate.

b. An assumption that a specific proportion of the PM-related premature mortality incidences are incurred by people with pre-existing Chronic Obstructive Pulmonary Disease (COPD) and that these incidences are associated with a loss of six months of life, regardless of age at death. If these values are not valid, what values would be more appropriate? Do you recommend a sensitivity analysis of 1 to 14 years (with the latter based on standard life tables), as included in the draft regulatory impact analysis of the proposed Nonroad diesel rule?

c. An assumption that the non-COPD incidences of PM-related premature mortality are associated with a loss of five years of life, regardless of age at death. If these values are not valid, what values would be more appropriate? Do you recommend a sensitivity analysis of 1 to 14 years (with the latter based on standard life tables), as included in the draft regulatory impact analysis of the proposed Nonroad diesel rule?

d. Additional quantified and/or monetized effects are those presented as sensitivity analyses to the primary estimates or in addition to the primary estimates, but not included in the primary estimate of total monetized benefits. While no causal mechanism has been identified for chronic asthma and ozone exposure, there is

suggestive epidemiological evidence.

i. Two studies suggest a statistical association between ozone and new onset asthma for two specific groups: children who spend a lot of time exercising outdoors and non-smoking men. We seek SAB comment on our approach to quantifying new onset asthma in the sensitivity analyses.

ii. Premature mortality associated with ozone is not currently separately included in the primary analysis because the epidemiological evidence is not consistent. We seek SAB comment on our approach to quantifying ozone mortality in the sensitivity analyses.

iii. Does the Council agree that there is enough data to support a separate set of health impacts assessment for asthmatics? If so, does the approach proposed by the Agency address the uncertainty in the literature?

HES Response: In regard to question 17.a., the HES recommend that the Alternative Estimate be dropped from the Section 812 analysis for several reasons. First, it gives a zero probability to the mortality effects of long-term exposure and in doing so, seriously underestimates the effects of air pollution. Second, there is little logic to providing a new low estimate without providing an accompanying new high estimate. As an alternative, the HES recommends that high and low estimates come from using the standard error around the existing CR functions including that using Pope et al., 2002 for premature mortality. The HES agrees with use of the cohort mortality studies for the base case estimate because this study design is capable of capturing effects of long-term PM exposure that the time series study design simply cannot capture. In the view of the HES, the selection process that EPA has used to develop the base case health estimates for PM provides a prudent estimate based on sound scientific evidence of effects. Although there is considerable uncertainty in the estimate for many reasons, it is not a worst case estimate and it may be either higher or lower than the true effects. Therefore, the HES does not agree that the use of the time series mortality studies, adjusted for a distributed lag, is an acceptable single alternative estimate to the base case estimate.

In regard to questions17.b. and c., which concern estimates of life-years lost, the HES notes that in the non-road diesel rule benefits assessment, life-years lost is calculated only in the alternative estimate, which is only for short-term exposure mortality. Causes of death are separated into COPD and non-COPD and in both cases it is assumed that the affected individuals had serious pre-existing and life shortening chronic illness. This is a strong assumption (that everyone who dies from PM has severe pre-existing disease). Although it may be more defensible for the short-term exposure mortality (but even there it is probably too strong), it should not be applied to the mortality estimates based on cohort studies.

If the life years lost calculations are going to be made for the short-term exposure mortality, the justification for the estimates of remaining life expectancy of 6 months (for COPD deaths) and 5-years (for non-COPD deaths) needs better documentation or at least discussion, especially for the assumption that it is invariant with age.

For calculating life-years lost for the cohort studies, the Subcommittee recommends contacting researchers using the ACS and the 6-cities data to see if they might have life-years lost

estimates available based on their data. If not, the Subcommittee recommends staying with the life-years lost estimation procedure used in the first prospective analysis based on standard life tables. This assumes that in the absence of the PM exposure life expectancy would have been the same as the average for others of the same age and gender (which includes an average number of people with chronic disease). Supporting this assumption, the Subcommittee points to evidence from the ACS reanalysis that the mortality risk is no greater for those with pre-existing illness at the time of enrollment in the study (Krewski et al., 2000) .

In regard to question 17.d.i., which concerns methods for quantifying new onset asthma, the Subcommittee agrees that ,so far, there are only two studies suggesting an effect of ozone on new onset (incidence) of asthma. Findings suggest some complex interactions of exposure and time-activity patterns outdoor, and the asthma literature indicates that onset of asthma depends on a variety of interacting factors, which may in addition change with age. Other air pollution studies are not conclusive on the issue. Thus, the HES proposes to disregard onset of asthma in the quantitative approach. The issue may be discussed qualitatively. The exclusion of this outcome may lead to some underestimation of the overall benefits.

In regard to question17.d.iii, concerning a separate asthma analysis, there is some appeal to looking at a subgroup that may have greater sensitivity to pollution exposure than the general population and those with asthma are a reasonable group to choose. However, with the recommendation that asthma exacerbation be added back into the primary set of C-R functions the need for this is reduced.

Agency Charge Question 29: Plans for Expert Elicitation Pilot for Premature Mortality

Charge Question 29. Does the Council support the plans described in chapter 9 for the expert elicitation pilot project to develop a probability-based PM2.5 C-R function for premature mortality, including in particular the elicitation process design? If the Council does not support the expert elicitation pilot project, or any particular aspect of its design, are there alternative approaches the Council recommends for estimating PM-related mortality benefits for this analysis, including in particular a probabilistic distribution for the C-R function to reflect uncertainty in the overall C-R function and/or its components?

HES response: The charge question asks the Council to respond to the preliminary design for a proposed pilot study using expert judgment to better characterize the uncertainty in the PM2.5 concentration-response function for premature mortality and to comment on specific aspects of the design of the pilot study. Further the charge question asks the Council to propose alternatives to expert judgment if it does not endorse the pilot project.

The HES strongly supports the use of expert judgment as a means of systematically characterizing the state of knowledge about the likely health impacts of changes in PM2.5 concentrations. The Subcomittee fully endorses the view espoused by the recent NAS Committee on Estimating the Health Benefits of Air Pollution Regulations that the question is not whether expert judgment will be used, but how it will be used.

The specific pilot project in expert judgment that the HES was asked to review proposes to use expert judgment to "address uncertainty in the aggregate C-R relationship" for PM2.5. The analytical plan indicates that this analysis is intended to produce results by December 2003.

The materials describing this proposal consist of a little more than a two pages of text. The broad elements of the general processes for the use of expert judgment are described briefly. The materials provided reflect an awareness of the literature in this field; and follow generally accepted practice in the field. However supporting details of the design of the pilot study are not provided.

In any proposed application of expert judgment, the major issues in the design of the study are – (a) definition of the question(s) to be elicited; (b) specification of the pool of relevant expertise and choice of an approach for identification and selection of experts; (c) deciding what materials to include in a briefing book; (d) deciding whether to hold a workshop at which the evidence can be reviewed and the procedures for eliciting expert judgment and potential issues in expert judgments can be introduced; (e) developing a protocol for eliciting judgments and determining: (i) whether an aggregate question or a set of disaggregated questions will be used; (ii) if a disaggregated approach is used determining the order of the questions and how to deal with correlated answers; and (iii) deciding whether elicitation aids (such as probability wheels) will be used; (f) determining whether efforts will be made to check the internal consistency of the judgments, and (g) deciding whether and how judgments will be combined, and if so, what information will be used in combining judgments (e.g., performance on calibration questions, peer or self ratings).

The EPA is to be commended for its efforts to deal with all of these issues and for its interest in the potential use of expert judgment to inform regulatory decision making. However, without having the opportunity to review more detailed documents – such as the draft elicitation protocol, the criteria used in expert selection, the briefing book, or the procedures proposed for calibration and combination of expert judgments – the HES is left with many questions.

1) Perhaps the most important question has concerns clear definition of the goal of the pilot project. Is it intended primarily to allow the Agency to gain experience with the formulation and conduct of expert judgment exercises? Or is it intended to provide information useful for near-term policy analyses, such as the off-road diesel rule? The potential utility of the pilot study depends heavily on its purpose.

2) Secondly, what is the scope of the question to be addressed by the pilot expert judgment? Is the exercise to produce a concentration-response function for PM2.5 mass (without regard to source), or is it intended to address differential relative toxicity? Is the concentration-response function intended to represent the response averaged across the US (without regard to background levels of PM2.5 and other pollutants), or is it intended to be applied to specific regions of the US (allowing for background levels of PM2.5 and co-pollutants)? Or are the results intended to be applied more broadly (e.g., outside of the US)?

3. Thirdly, what criteria will be used in the selection of experts? The EPA has indicated that it is considering relying on experts selected from two recent NAS panels which have dealt extensively with airborne particulate matter.

The HES agrees that the use of experts from recent NAS panels has several potential advantages: (1) These experts have already been selected by their peers for service on NAS panels; and (2) They may be a bit more detached from the original research than the primary investigators and may be able to evaluate evidence with more objectivity than the original investigators.

However, there are still unanswered questions. Some pertain to the disciplinary mix of the experts asked to participate in the study. What will be the balance of epidemiologists, toxicologists, basic biologists, clinicians? Will experts who are familiar with the diesel PM-lung cancer literature (e.g., the railroad workers studies) be included as well as experts familiar with cohort and time series studies of ambient PM? Will experts in cardiovascular disease or cancer be included (they might be able to address issues of mechanism, latency and impact on life expectancy)?

Another unanswered question concerns why was the decision made to use a single composite (or aggregate) question – e.g., "What reduction in mortality would be expected from a 1 ug/m3 reduction in PM2.5 across the entire US?" While some members of the HES understand the EPA's preference for using an "aggregate" question in the pilot study, others on the committee would prefer that a disaggregated approach be used instead. This is in part because there is concern that some analysts using the results may be frustrated if they cannot understand the reasoning used by the experts to develop their characterizations of the state of knowledge. Many experts in the field argue that the quantitative answers are less important than the insights produced. In this spirit, the HES recommends that narrative descriptions of the rationale used by each expert are collected and presented along with the quantitative characterizations of uncertainty and that in the second stage of the work that a disaggregated approach be used.

- An additional question concerns exactly how the elicitation questions, briefing book and protocol will be developed. The HES believes that the development of the briefing book and the elicitation protocol should be developed in an iterative process involving extensive interaction with the selected experts, the domain expert and the elicitor(s).

In addition, the proposal is not clear about how the individual expert judgments will be aggregated. The HES advises the EPA to present first the entire collection of individual judgments, and then to follow the advice of Morgan and Henrion (CITATION?). If the individual judgments are aggregated, the HES urges the EPA to present both simple (equal weight) aggregations and more complex (calibration weighted) versions of the results, but to stress that the user of the information must be aware of the entire spectrum of results.

The HES acknowledges the view that some may recommend that the individual judgments be adjusted for any over- (or under-) confidence evident in individual experts' performance on calibration questions. While many of us agree that in principle this might be desirable, the HES

does not recommend this approach– largely because its validity depends so much on the relevance of the calibration questions to the real issue of interest, but also because it may be politically impractical. Domain experts may be hesitant to participate in, or broadly support, the use of expert judgment if they feel that their opinions will be discounted or manipulated. If broader use of expert judgment to inform public policy decisions is to occur, this approach must be avoided.

In addition, the materials provided to the HES appear to indicate that experts may be asked how to weight the results from time-series and cohort studies. The HES strongly disagrees with this approach. Cohort and time-series studies measure two different effects. They should not be viewed as alternative sources of evidence, but as complimentary sources of evidence. Both should be elicited, but separately. If resources permit only one effect to be elicited, the focus should be on cohort mortality.

Finally, the HES urges the EPA to recognize the limitations of expert judgment as well as its strengths. While the HES strongly supports this effort to use expert judgment to characterize uncertainty in benefits estimates underlying a major regulation, it is important to be honest about the limitations of the method. There are questions that this method can not usefully address. These are questions where both theory and data are so inadequate that there is no basis for knowing how little is known. McKone and others (CITATION???) have used the term "ignorance" to distinguish this situation from "uncertainty." While there are varying opinions within the HES about which issues fall into which category, many members are somewhat hesitant about using expert judgment to identify concentration-response thresholds for PM. On the other hand, most of us believe that questions about the "differential toxicity" of particles from various emissions sources can be usefully addressed with the method. Having said this, the HES notes that many decision analysts would argue that it is exactly in situations where little is known that expert judgment is most appropriate.

In summary, the HES enthusiastically supports the use of expert judgment to inform policy analysis; commend the EPA for moving in this direction; understand their hesitancy to move too quickly; support the pilot study; question whether it is advantageous to use the results of the pilot study in support of a major regulatory initiative; seek much more detailed information about the details of the proposed approach; advise that the process (BUT NOT THE RESULTS) be subjected to careful peer review; and urge the EPA to invest adequate resources, time, and managerial attention to further development of this approach so that it can be used to inform this Second Prospective Analysis.

Should the Agency wish to conduct a more comprehensive peer review of the process proposed for elicitation of expert judgment, it is the recommendation of the HES that any review group include at least three persons, with expertise in the following areas: (a)Uncertainty analysis, particularly the processes for the formal elicitation of expert judgment; (b) Epidemiology, with some sympathy for the use of subjective judgment in the formal characterization of uncertainty in the interpretation of studies; and (c)The Domain of Interest – i.e., cohort and time-series studies of mortality induced by particulate matter.

<u>Agency Charge Question 30: Plans for Estimating Independent Effects of Ozone Mortality</u>

Charge Question 30. EPA plans to develop estimates of an independent mortality effect associated with ozone, as described in chapter 9. Does the Council support the use of the most recent literature on the relationship between short-term ozone exposure and daily death rates, specifically that portion of the literature describing models which control for potential confounding by PM2.5? Does the Council agree with the use of that literature as the basis for deriving quantified estimates of an independent mortality impact associated with ozone, especially in scenarios where short-term PM2.5 mortality estimates are used as the basis for quantifying PM mortality related benefits? Does the Council support the plans described in chapter 9 for the pilot project to use this literature to develop estimates of the ozone related premature mortality C-R function using the three alternative meta-analytic approaches? If the Council does not support this pilot project, or any particular aspect of its design, are there alternative approaches to quantifying ozone-related premature mortality which the Council recommends?

HES Response: Acute ozone effects is an important yet complex issue that needs to be addressed as EPA moves forward with benefits analyses. A large and growing literature exists on ozone mortality associations with and without control of PM covariates. However, the interpretation of these results is made complicated by several issues, including possible confounding by PM, effect modification by season and interactions with temperature and other weather factors. Thus, the effects are hard to ignore, but their interpretation remains problematic, raising questions as to how best to incorporate these effects into the benefits analysis. The Subcommittee endorses EPA's plans to sponsor three new meta analyses of ozone impacts. This will yield information on the consistency of the effects of ozone and to what extent they are independent of PM. While the HES agrees with EPA that PM2.5 is the most important co-pollutant to be concerned about, the meta analyses should not necessarily be limited to only those ozone studies that have PM2.5 data. Other studies may also be informative, including those using PM10, estimated PM2.5, and/or optical measures of blackness. The Subcommittee looks forward to reviewing the results of these meta analysis results.

Agency Charge Question 32: Evaluating Data Quality and Plans for Publication of Intermediate Data Products

Agency Charge Question 32. Does the Council support the plans described in chapter 10 for evaluating the quality of data inputs and analytical outputs associated with this study, including the planned publication of intermediate data products and comparison of intermediate and final results with other data or estimates? If the Council does not support these plans, are there alternative approaches, intermediate data products, data or model comparisons, or other data quality criteria the Council recommends? Please consider EPA's Information Quality Guidelines in this regard.

HES Response: The Subcommittee enthusiastically supports EPA's plan to make available through EPA's web site the intermediate information and data products produced in the course of the 812 analysis. The BENMAP system demonstrated to the Subcommittee appears to be an invaluable tool for both generation and facilitation of a widespread understanding of the

analysis and its results. In particular it will enhance understanding of the assumptions used in constructing the aggregates of results, and the consequences of alternative aggregation approaches and assumptions.

It might be of interest to assess the degree of "surprise"—where possible compare the extent of each change with the prior belief about the uncertainty in the estimate. Historically, even in fields with well established procedures for estimating uncertainties (such as measurements of elementary particle masses by physicists), it is found that traditional statistical procedures for estimating standard errors, etc. systematically understate actual uncertainties as later calculated by comparing improved measurements with older measurements and previously estimated uncertainties (for examples see the references provided below). This is because traditional statistical uncertainty estimation approaches tend to be based solely on random sampling-error uncertainties in the data, neglecting what frequently turns out to be appreciable systematic or calibration errors (See Shlyakhter references below). Developing fair estimates of uncertainties for the CAAA benefit and cost projections will require analysts to have inputs that can be interpreted in terms of both types of uncertainty. Systematic evaluation of the extent and reasons for changes in successive sets of emissions estimates will be a start toward providing invaluable inputs to the overall uncertainty analysis.

The HES also suggests that there is some value in having clearly stated data quality objectives (DQOs) and a specific comprehensive data quality assurance (QA) protocol. These objectives should be derived from the context of the 812 analysis and should guide the design and presentation of the intermediate data projects to best serve the needs of specific audiences for the data. Discussion among the group identified two broad types of users whose differing needs should be kept in mind: (1) policy and staff advisors whose main goal may be to just understand the basis of the 812 analysis and its conclusions, and also (2) highly sophisticated analysts who wish to do their own professional evaluations of specific risk and benefit issues based on some of the data generated by EPA and its 812 analysis contractors. With the needs of these two groups in mind, the disclosure and ready availability of the intermediate data products, presented on the website and otherwise in context along with a summary of the DQOs, should greatly enhance the value of the 812 analysis for both public and private sector decision-makers.

Agency Charge Question 33: Plans for aggregation and presentation of analytical results from the Health Analysis

Charge Question 33: Does the Council support the plans described in Chapter 11 for the aggregation and presentation of analytical results from this study? If the Council does not support these plans, are there alternative approaches, aggregation methods, results presentation techniques, or other tools the Council recommends?

HES Response: For the first prospective study, EPA compared costs to benefits for the years 2000 and 2010. The Agency also aggregated the net present value of costs and benefits for the 1990 through 2010 period. The approach was to use a linear interpolation between the years 1990 and 2000 and a second linear interpolation between 2000 and 2010. The linear interpolation was used because air quality modeling was only carried for the years 2000 and 2010.

The modeling results for the first study supported estimates of annual and cumulative costs for Titles I through V and annual estimates for Title VI. The benefits were not disaggregated by Title nor, with some minor exceptions, were they disaggregated by geographic area, although spatially disaggregated data were presented in the report appendices.

a) Alternative approaches: The formal probability analysis method will eventually be used to provide better estimated of uncertainty and estimations of model sensitivity to modeled factors. This may be superior to the use of comparing results of applying different analytical methodologies to assess uncertainty.

b) Aggregation methods: There are only a few C-R functions for source-specific health effects and therefore limited information for sector specific PM health benefits or for apportioning health benefits among sources or sectors other than as a function of source-specific contributions to ambient PM mass. With the exception of particle size considerations, the toxicity of all PM is treated as equivalent regardless of its origin. (however, one could do some limited sensitivity analysis using available results –do we want to suggest this?

(1) Sectoral Disaggregation – The plan for generating sector-specific benefit results involves independent scenarios that selectively omit emissions reductions for a single sector (i.e. holding emissions at pre-CAAA levels) while bringing all other sectors to their post-CAAA levels. The issues of emissions estimates and transport will be evaluated by the Air Quality Modeling Subcommittee, but the estimates will presumably include data to compute exposures to both fine and coarse mode particles. These exposures can then be used in conjunction with appropriate C-R functions to estimate health benefits by sector.

(2) Spatial Disaggregation – The cost and benefit modeling for spatial disaggregation will be presented in the Appendix. There are limitations in ability to accurately predict population growth patterns on a spatial level over several years. Also on a regional level areas which incur pollutant abatement costs may be different from areas that receive health benefits. Spatially disaggregated health benefits can be estimated but because of the mismatch with costs, it may be difficult to interpret the disaggregated net benefits. The cost issues will be addressed separately by the Council.

(3) Pollutant Endpoint Disaggregation – In cases where endpoint-pollutant combinations can be identified that can be associated with a specific benefit, disaggregated benefits can be presented. Detailed statistical analyses to identify pollutant interactions have been used in apportioning air pollution contributions among sources. The possibility of using such source-receptor methods for disaggregating health effects among pollutant combinations may be possible.

c) Presentation techniques: EPA plans to estimate costs, benefits and net benefits for the years 2000, 2010 and 2020. They will also calculate benefit/cost ratios, although the Council's

comments on the 2001 draft analytical plan indicated a 'preference for net benefit estimates.' Taken by themselves, ratios can be misleading and it was not clear in the plan how these ratios would be used. It would seem that use of these ratios would require very detailed explanations and unless there is some specific benefit to their inclusion, it might be better to leave them out.

Agency Charge Question 34: Plans for Stratospheric Ozone Analysis

Charge Question 34. Does the Council support the plans describe in Appendix E for updating the estimated costs and benefits of Title VI programs? If the Council does not support these plans, are there alternative data, models, or methods the Council recommends?

HES Response: The proposed revised approach to determining costs and benefits of controls to limit stratospheric ozone reductions by anthropogenic chemicals is basically sound, and addresses the issue comprehensively. Recent advances in knowledge and models make it possible to address the issue with somewhat greater confidence, while still recognizing that great uncertainties remain concerning both scientific and economic assumptions and constraints when dealing with a time frame extending to 2075. Overall, the Subcommittee concludes that the plans make quite reasonable assumptions and choices.

The Subcommittee suggests that the text be revised to provide more information on two points: (1) the basis for the effects coefficient for cataract formation, and (2) the basis for the effects coefficient for basal cell carcinoma and malignant melanoma. The Subcommittee also suggests the following specific comments to strengthen Appendix E: (1) on page E-4, the judgment that unquantified ecological benefits are minimal compared to the benefits estimated by the AHEF model could be correct, but needs to be better justified, and (2) on page E-6, shouldn't "ozone depletion" be replaced by "ODS control"? Additionally, the text needs to clarify the source of the cataract data to be used (in the public meeting, EPA staff said it was the National Eye Institute data base) and any sample size or other issues with the data that would raise concerns about its use for this analysis. Although the state of the science is not well-developed, the levels of uncertainty in both the cancer and cataract data need to be described and their potential impacts on the cost-benefit analysis discussed. Mention of the limitations and/or lack of data from animal models relevant to specific human outcomes (e.g., basal cell carcinoma, malignant melanoma, etc.) would strengthen this section.

Agency Charge Question 35: Plans for an Air Toxic Case Study

Charge Question 35. Does the Council support the plans described in Appendix E for the benzene case study, including the planned specific data, models, and methods, and the ways in which these elements have been integrated? If the Council does not support these plans, are there alternative data, models, or methods the Council recommends?

HES Response: The Subcommittee notes that the basic conception of the case study is reasonable, given that the chemical chosen is data rich, and therefore not a typical air toxic. Several suggestions for strengthening the approach follow. The plan for deriving the concentration response function mentions only an analysis of a relatively small (only 9 leukemia

cases) and older epidemiology study (Crump et al., 1994). The current plan neglects much newer and more extensive leukemia and supporting chromosome breakage, and other genetic biomarker exposure response data collected by U.S. researchers among large numbers of Chinese workers with a broad range of exposures (Hayes et al., 2000, 1997; Rothman et al., 1995, 1996ab, 1997.) The exposure estimates used in these studies have been criticized (Wong, 1999), however further work with the authors of the study seems likely to be able to produce dose response information that is at least equal to, and likely superior to, that which is the basis of the older benzene cancer potency estimates. One particularly important implication of the newer information is that in contrast to the suggestion of an upward turning curve from the older higher dose data, the newer data seem to indicate a convex dose response shape (linear at low doses, with some fitting at higher dose rates) consistent with the idea that there is high dose saturation of the generation of some genetically active activated intermediate metabolite—most likely one produced by a specific P450 enzyme (Rothman et al., 1997).

The HES also suggests that EPA also considers and reviews other well-conducted studies, especially where these have been conducted at exposure levels closer to what the general public may experience [e.g. Rushton and Romaniuk (1997); OEM: 54,152-166; and Schnatter et al. (1996); OEM: 53, 773-781]. Uncertainty assessment should include consideration of extrapolation from high-exposure studies of adult (usually male) workers, to the lower exposures and more diverse population of the general public.

In regard to the data to be used, the 1990 data, measured by Texas Natural Resource Conservation Commission, will be used as the base case (pre-CAAA). The 1999 NTI could be used as a surrogate for the 2000 (post-CAAA) data, however it might be more consistent to project the data to 2000. Four options for incorporating CAAA impacts were offered. Option 2 takes into account MACT expectations as well as impact of the Houston Ozone State Implementation Plan (SIP) provisions, but Option 3 which uses existing EPA databases might be easier to implement.

The plan to limit the case study to the Houston area makes sense for this first cut. If the benefits turn out to be non-negligible, a broader application of the case study might be warranted. Extension to Portland and/or Philadelphia should depend on the Houston outcome.

Agency Charge Question 36. A cessation lag for benzene-induced leukemia is difficult to estimate and model precisely due to data limitations, and EPA plans to incorporate a five-year cessation lag as an approximation based on available data on the latency period of leukemia and on the exposure lags used in risk models for the Pliofilm cohort (Crump, 1994 and Silver et al., 2002). Does the SAB support adoption of this assumed cessation lag? If the Council does not support the assumed five-year cessation lag, are there alternative lag structures or approaches the Council recommends?

HES Response: The simple lag interpretation of 5 years mentioned in the blueprint does not seem to utilize all the material in the original Crump (1994) paper--in particular an equation (utilizing the parameter K) that Crump uses to weight exposures that occurred at different times relative to the appearance of the leukemias. Some finite minimum lag is likely to be justified by

the growth rate of tumors from initial single cells to the point at which there are enough cells to be clinically detectable as a cancer. This issue needs to be revisited in the light of a more recent analysis of data from the original U.S. cohort (Silver et al., 2002) as well as observations of the distributions of excess tumors in studies of radiation-induced leukemias. If available, data from the NCI-Chinese studies (cited above) should also be analyzed for differences in the timing of exposures and the timing of the appearance of tumors.

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APPENDIX A
List of Charge Questions Provided to the HES

Listed below are the charge questions addressed by the Health Effects Subcommittee of the Advisory Council in Clean Air Compliance Analysis in this report.

Charge Question 11. Does the Council support the plans described in chapter 6 for estimating, evaluating, and reporting changes in health effect outcomes between scenarios? If there are particular elements of these plans which the Council does not support, are there alternative data or methods the Council recommends?

Charge Question 12. EPA seeks advice from the Council regarding the technical and scientific merits of incorporating several new or revised endpoint treatments in the current analysis. These health effect endpoints include:

a. Premature mortality from particulate matter in adults 30 and over, PM (Krewski et al., 2000);
b. A PM premature mortality supplemental calculation for adults 30 and over using the Pope 2002 ACS follow-up study with regional controls;
c. Hospital admissions for all cardiovascular causes in adults 20-64, PM (Moolgavkar et al., 2000);
d. ER visits for asthma in children 0-18, PM (Norris et al., 1999);
e. Non-fatal heart attacks, adults over 30, PM (Peters et al., 2001);
f. School loss days, Ozone (Gilliland et al., 2001; Chen et al., 2000);
g. Hospital admissions for all respiratory causes in children under 2, Ozone (Burnett et al., 2001); and,
h. Revised sources for concentration-response functions for hospital admission for pneumonia, COPD, and total cardiovascular: Samet et al., 2000 (a PM10 study), to Lippmann et al., 2000 and Moolgavkar, 2000 (PM2.5 studies).

Charge Question 13. EPA seeks advice from the Council regarding the merits of applying updated data for baseline health effect incidences, prevalence rates, and other population characteristics as described in chapter 6. These updated incidence/prevalence data include:

a. Updated county-level mortality rates (all-cause, non-accidental, cardiopulmonary, lung cancer, COPD) from 1994-1996 to 1996-1998 using the CDC Wonder Database;
b. Updated hospitalization rates from 1994 to 1999 and switched from national rates to regional rates using 1999 National Hospital Discharge Survey results;
c. Developed regional emergency room visit rates using results of the 2000 National Hospital Ambulatory Medical Care Survey;
d. Updated prevalence of asthma and chronic bronchitis to 1999 using results of the National Health Interview Survey (HIS), as reported by the American Lung Association (ALA), 2002;
e. Developed non-fatal heart attack incidence rates based on National Hospital Discharge Survey results;

f. Updated the national acute bronchitis incidence rate using HIS data as reported in ALA, 2002, Table 11;
g. Updated the work loss days rate using the 1996 HIS data, as reported in Adams, et al. 1999, Table 41;
h. Developed school absence rates using data from the National Center for Education Statistics and the 1996 HIS, as reported in Adams, et al., 1999, Table 46.
1. Developed baseline incidence rates for respiratory symptoms in asthmatics, based on epidemiological studies (Ostro et al. 2001; Vedal et al. 1998; Yu et al; 2000; McConnell et al., 1999; Pope et al., 1991).

Charge Question 14. EPA plans to initiate an expert elicitation process to develop a probability-based method for estimating changes in incidence of PM-related premature mortality. Plans for this expert elicitation are described in chapter 9 of this blueprint, and a separate charge question below requests advice from the Council pertaining to the merits of the design of this expert elicitation. EPA recognizes, however, the possibility that this expert elicitation process may not be fully successful and/or may not be completed in time to support the current 812 analysis. Therefore, in order to facilitate effective planning and execution of the early analytical steps which provide inputs to the concentration-response calculations, EPA seeks advice from the Council regarding the scientific merits of alternative methods for estimating the incidences of PM-related premature mortality, including advice pertaining to the most scientifically defensible choices for the following specific factors:

a. Use of cohort mortality studies, daily mortality studies, or some combination of the two types of studies
b. Selection of specific studies for estimating long-term and/or short-term mortality effects
c. Methods for addressing –either quantitatively or qualitatively– uncertain factors associated with the relevant concentration-response function(s), including
i. Shape of the PM mortality C-R function (e.g., existence of a threshold),
ii. PM causality,
iii. PM component relative toxicity, and
iv. PM mortality effect cessation lag structure
v. Cause of death and underlying health conditions for individuals dying prematurely due to chronic and/or short term exposures to particulate matter
vi. The use of ambient measures of exposure for estimating chronic health effects, given recent research reviewed in the NAS (2002) report that questions the implications of using ambient measures in cohort studies

Charge Question 15. EPA estimates of benefit from particulate control may underestimate the impact of nonfatal cardiopulmonary events on premature mortality and life expectancy. For the base analyses, which rely on cohort evidence, the limited follow-up periods for the cohorts may not fully capture the impacts of nonfatal cardiovascular events on premature mortality later in life. For the alternative analyses –including cost-effectiveness analyses– which rely more on acute studies and life-expectancy loss, the years of life are estimated only for fatal events. Yet nonfatal events such as myocardial infarction reduce a person's

life expectancy by a substantial percentage.

a. Do you agree that EPA, in the 812 analyses, should adjust benefit estimates to account for the mortality effects of non-fatal cardiovascular and respiratory events?

b. What medical studies and mathematical models of disease might be useful to review or use if EPA moves in this direction?

c. When the nonfatal events are valued in economic terms, should EPA assume that the published unit values for morbidity already account for the life-expectancy loss or should an explicit effort be made to monetize the resulting longevity losses?

Charge Question 16. In recent EPA rulemakings, EPA's "base estimate" of benefit from PM control has been based on cohort epidemiological studies that characterize the chronic effects of pollution exposure on premature death as well as capturing a fraction of acute premature mortality effects. If these chronic effects occur only after repeated, long-term exposures, there could be a substantial latency period and associated cessation lag. As such, a proper benefits analysis must consider any time delay between reductions in exposure and reductions in mortality rates. For the acute effects, such as those considered in EPA's alternative benefit analyses, the delays between elevated exposure and death are short (less than two months), and thus time-preference adjustments are not necessary.

a. In the previous 812 analysis and in recent rulemakings, EPA assumed a weighted 5-year time course of benefits in which 25% of the PM-related mortality benefits were assumed to occur in the first and second year, and 16.7% were assumed to occur in each of the remaining 3 years. Although this procedure was endorsed by SAB, the recent NAS report (2002) found "little justification" for a 5-year time course and recommended that a range of assumptions be made with associated probabilities for their plausibility. Do you agree with the NAS report that EPA should no longer use the deterministic, 5-year time course?

b. One alternative EPA is considering is to use a range of lag structures from 0 to 20-30 years, with the latter mentioned by NAS in reference to the Nyberg et al PM lung cancer study, with 10 or 15 years selected as the mid-point value until more definitive information becomes available. If this simple approach is used, should it be applied to the entire mortality association characterized in the cohort studies, or only to the difference between the larger mortality effect characterized in the cohort studies and the somewhat smaller effect found in the time series studies of acute exposure? Should judgmental probabilities be applied to different lags, as suggested by NAS?

c. Another option under consideration is to construct a 3-parameter Weibull probability distribution for the population mean duration of the PM mortality cessation lag. The Weibull distribution is commonly used to represent probabilities based on expert judgment, with the 3-parameter version allowing the shaping of the probability density function to match expected low, most likely, and expected high values. EPA is still considering appropriate values for the low, most likely, and expected high values –and therefore for the Weibull shape and location parameters– and EPA is interested in any advice the Council wishes to provide pertaining to the merits of this approach and/or reasonable values for the

probability distribution.

Charge Question 17. In support of Clear Skies and several recent rule makings the Agency has presented an Alternative Estimate of benefits as well as the Base Estimate. EPA developed the Alternative Estimate as an interim approach until the Agency completes a formal probabilistic analysis of benefits. NAS (2002) reinforced the need for a probabilistic analysis. The Alternative Estimate is not intended as a substitute method and needs to be considered in conjunction with the Base Estimate. Presentation of Base and Alternative estimates in the 812 Report may not be necessary if the probability analysis planned for the 812 Report is successful. While the Base Estimate assumes that acute and chronic mortality effects are causally related to pollution exposure, the Alternative Estimate assumes only acute effects occur or that any chronic effects are smaller in size than assumed in the Base Estimate. The Council's advice is sought on the following matters:

a. It has been noted by some particle scientists that the size of estimates based on time series studies that incorporate a distributed lag model, accounting for effects of 30 to 60 days after elevated exposure, may be similar in size to some interpretations of the results from the cohort studies. Does the Council agree that it is a reasonable alternative to use an estimate of the concentration-response function consistent with this view? If the Council agrees with the assumption, can it suggest an improved approach for use in an Alternative Estimate? The agency also seeks advice on appropriate bounds for a sensitivity analysis of the mortality estimate to be used in support of the Alternative Estimate.

b. An assumption that a specific proportion of the PM-related premature mortality incidences are incurred by people with pre-existing Chronic Obstructive Pulmonary Disease (COPD) and that these incidences are associated with a loss of six months of life, regardless of age at death. If these values are not valid, what values would be more appropriate? Do you recommend a sensitivity analysis of 1 to 14 years (with the latter based on standard life tables), as included in the draft regulatory impact analysis of the proposed Nonroad diesel rule?

c. An assumption that the non-COPD incidences of PM-related premature mortality are associated with a loss of five years of life, regardless of age at death. If these values are not valid, what values would be more appropriate? Do you recommend a sensitivity analysis of 1 to 14 years (with the latter based on standard life tables), as included in the draft regulatory impact analysis of the proposed Nonroad diesel rule?

d. Additional quantified and/or monetized effects are those presented as sensitivity analyses to the primary estimates or in addition to the primary estimates, but not included in the primary estimate of total monetized benefits. While no causal mechanism has been identified for chronic asthma and ozone exposure, there is suggestive epidemiological evidence.

   i. Two studies suggest a statistical association between ozone and new onset asthma for two specific groups: children who spend a lot of time exercising outdoors and non-smoking men. We seek SAB comment on our approach to quantifying new onset asthma in the sensitivity analyses.

   ii. Premature mortality associated with ozone is not currently separately

included in the primary analysis because the epidemiological evidence is not consistent. We seek SAB comment on our approach to quantifying ozone mortality in the sensitivity analyses.

iii. Does the Council agree that there is enough data to support a separate set of health impacts assessment for asthmatics? If so, does the approach proposed by the Agency address the uncertainty in the literature?

Charge Question 29. Does the Council support the plans described in chapter 9 for the expert elicitation pilot project to develop a probability-based PM2.5 C-R function for premature mortality, including in particular the elicitation process design? If the Council does not support the expert elicitation pilot project, or any particular aspect of its design, are there alternative approaches the Council recommends for estimating PM-related mortality benefits for this analysis, including in particular a probabilistic distribution for the C-R function to reflect uncertainty in the overall C-R function and/or its components?

Charge Question 30. EPA plans to develop estimates of an independent mortality effect associated with ozone, as described in chapter 9. Does the Council support the use of the most recent literature on the relationship between short-term ozone exposure and daily death rates, specifically that portion of the literature describing models which control for potential confounding by PM2.5? Does the Council agree with the use of that literature as the basis for deriving quantified estimates of an independent mortality impact associated with ozone, especially in scenarios where short-term PM2.5 mortality estimates are used as the basis for quantifying PM mortality related benefits? Does the Council support the plans described in chapter 9 for the pilot project to use this literature to develop estimates of the ozone related premature mortality C-R function using the three alternative meta-analytic approaches? If the Council does not support this pilot project, or any particular aspect of its design, are there alternative approaches to quantifying ozone-related premature mortality which the Council recommends?

Charge Question 32. Does the Council support the plans described in chapter 10 for evaluating the quality of data inputs and analytical outputs associated with this study, including the planned publication of intermediate data products and comparison of intermediate and final results with other data or estimates? If the Council does not support these plans, are there alternative approaches, intermediate data products, data or model comparisons, or other data quality criteria the Council reommends? Please consider EPA's Information Quality Guidelines in this regard.

Charge Question 33. Does the Council support the plans described in Chapter 11 for the aggregation and presentation of analytical results from this study? If the Council does not support these plans, are there alternative approaches, aggregation methods, results presentation techniques, or other tools the Council recommends?

Charge Question 34. Does the Council support the plans describe in Appendix D for updating the estimated costs and benefits of Title VI programs? If the Council does not support these plans, are there alternative data, models, or methods the Council recommends?

Charge Question 35. Does the Council support the plans described in Appendix E for the benzene case study, including the planned specific data, models, and methods, and the ways in which these elements have been integrated? If the Council does not support these plans, are there alternative data, models, or methods the Council recommends?

Charge Question 36. A cessation lag for benzene-induced leukemia is difficult to estimate and model precisely due to data limitations, and EPA plans to incorporate a five-year cessation lag as an approximation based on available data on the latency period of leukemia and on the exposure lags used in risk models for the Pliofilm cohort (Crump, 1994 and Silver et al., 2002). Does the SAB support adoption of this assumed cessation lag? If the Council does not support the assumed five-year cessation lag, are there alternative lag structures or approaches the Council recommends?